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## Editorial

# Vancomycin: Renewed Interest in an Old Drug

Vancomycin has been commercially available for over 20 years. Initially the drug was used as a primary agent to treat infections due to a variety of gram positive bacteria. In the mid-1960s and 1970s its use declined after the introduction of the semisynthetic penicillins and the cephalosphorins. Both were considered less toxic, and the cephalosporins had an extended spectrum which included many gram-negative organisms.

Over the last five years there has been renewed interest in vancomycin. Firstly, methicillin resistant *Staphylococcus aureus* infections have become endemic in many centers (1, 2). Secondly, *Staphylococcus epidermidis* infections are being seen with increased frequency (3). As many as 80 % of these strains are methicillin resistant (3). Thirdly, improved formulations which contain less impurities have been developed and the drug may be less toxic than when it was first introduced (4). Fourthly, orally administered vancomycin has become a primary agent in the treatment of pseudomembranous colitis.

### Pharmacokinetics

Vancomycin is not absorbed orally, and even patients with renal failure do not achieve significant serum levels when given the drug orally. However, oral administration of the drug does produce excellent levels in the stool of the distal colon. Vancomycin should not be given intramuscularly, as it causes severe pain; hence it must be given intravenously to treat systemic infections. The drug is reconstituted with 10 cc of sterile water, and then diluted with saline or glucose. It is very soluble after reconstitution at pH 4, but solubility decreases as the pH rises. In general, vancomycin should not be mixed with other drugs, particularly the beta-lactams, heparin, and sodium bicarbonate. The drug is excreted almost completely by the kidney in man, and there is no evidence of tubular reabsorption or secretion.

The pharmacokinetics of vancomycin are complex. Vancomycin elimination seems to fit best into a three compartmental model in adults (5). There is a rapid distribution phase which lasts about 10 minutes and is called the alpha half-life. This is followed by an intermediate half-life, and a beta elimination half-life of 5 to 10 hours. One gram given intravenously produces peak levels of 25 μg/ml, and therapeutic levels persist for 12 hours. On the basis of this data, vancomycin should be given at an interval of 8 to 12 hours to adults (5). The elimination half-life may be shorter in children over the age of 30 days, and the drug can be given to them at six hourly intervals. In patients with normal renal function the total daily dose is usually about 2 g per day.

The total volume of distribution is variable, but approximately 0.9 l/kg, indicating high tissue concentrations and extensive drug distribution. The volume of the central compartment is roughly 10 % of the volume of distribution and approximates the blood volume. Vancomycin is about 55 % protein bound (5). The clinical significance of this protein binding is unknown.

Because vancomycin excretion is totally dependent upon renal function, the dose must be altered in the presence of even a moderate degree of renal insufficiency. This is best accomplished by using the nomogram developed by Moellering (6). In patients undergoing hemodialysis, a dose of 15 mg/kg can be given every 7 to 10 days to produce adequate levels. Hemodialysis does not effectively remove vancomycin. Peritoneal dialysis is probably more effective in removing vancomycin, however, the amount removed appears to be insignificant (7). The drug can be given intravenously though in patients with peritonitis (7).

As one might expect from the volume of distribution vancomycin penetrates well into most body fluids, averaging 40–70 % of simultaneous serum levels. These include pleural, synovial, pericardial, and ascitic fluid. Unfortunately, penetration across the blood brain barrier is inadequate, particularly in adults (8). Experience is limited, but the drug has been given intrathecally and intraventricularly in doses of 10–20 mg/24 h. It also appears that vancomycin may cross the blood brain barrier to a greater extent in infants, however clinical experience using the drug to treat meningitis is extremely limited (8).

The pharmacokinetics of vancomycin during cardiopulmonary bypass surgery deserve special consideration (9). Vancomycin may be used as an alternative to the cephalosporins for prophylaxis during cardiac surgery. The frequently used dose of 500 mg (7 mg/kg) given preoperatively produces inadequate levels during bypass. This is due to a precipitous fall in the serum level directly after the initiation of cardiopulmonary bypass. Therefore, an initial dose of 15 mg/kg should be administered prior to surgery. Patients with normal renal function should be given a second dose of 10 mg/kg immediately after the completion of bypass to sustain adequate levels (9).

## Clinical Use

Vancomycin has been shown to be effective in the therapy of a wide variety of infections due to gram-positive organisms (Table 1). It is generally considered the drug of choice in the treatment of serious infections due to methicillin resistant staphylococci, both *Staphylococcus aureus* and *epidermidis*. Most authors feel that it is preferable to use vancomycin even when disc sensitivity testing suggests that the organism is sensitive to one of the cephalosporins. This is due to the large number of organisms that are subsequently demonstrated to be resistant or have resistant subpopulations when broth dilution MICs are done with a high inoculum. In addition, resistant subpopulations (heteroresistance) may require incubation at lower temperatures than are used in some laboratories (i.e. 30–35 °C).

Vancomycin is often used to treat staphylococcal infections in patients undergoing hemodialysis. The prolonged half-life of the drug in this setting makes it particularly convenient to use in the therapy of shunt infections and endocarditis. Weekly injections can be given to an outpatient without causing any interruption of the normal dialysis schedule. One study has even demonstrated that it is effective in preventing these infections when given prophylactically (10).

In recent years *Staphylococcus epidermidis* has emerged as a major pathogen in a number of clinical settings. It is now the most common cause of prosthetic valve endocarditis, endophthalmitis, and prosthetic hip infections. In addition, intravenous catheter related infections are being seen with increased frequency. Karchmer and coworkers have demonstrated that the overwhelming majority of nosocomial *Staphylococcus epidermidis* infections are caused by methicillin resistant organisms (3). Therefore, vancomycin has become the backbone of therapy directed against these infections. Vancomycin is still used as an alternate drug in the therapy of a number of serious infections, most notably endocarditis and sepsis. Patients with viridans streptococcal endocarditis who are allergic to penicillin can be effectively treated with vancomycin alone. However, it should be pointed out that the drug is not bactericidal against enterococci, and must be used in combination with an aminoglycoside in the therapy or prophylaxis of enterococcal endocarditis. It can also be used prior to dental work as a prophylactic agent. One gram is administered intravenously prior to the procedure, and it is followed by the oral administration of 500 mg of erythromycin every six hours for eight doses (11).

In recent years vancomycin has been used with increased frequency in the therapy of pseudomembranous colitis. The drug can be given orally for this purpose and is essentially free of toxicity when used in this manner. It appears that a dose of 125 mg given four times per day is sufficient, with the length of therapy ranging from five to ten days. Patients who are too ill to take the drug orally can be treated with intravenously administered drug if necessary.

Finally, vancomycin may be used to treat a variety of other infrequently occurring gram-positive infections. It is a primary agent in the therapy of serious diphtheroid infections. These organisms may cause prosthetic valve endocarditis and are usually resistant to most other antimicrobials. It may also be used as an alternative agent in the treatment of other streptococcal infections. The drug has poor activity against gram-negative organisms and most obligate anaerobes are resistant.

Table 1: Spectrum of activity of vancomycin.

| |
|---|
| *Staphylococcus aureus* |
| *Staphylococcus epidermidis* |
| Streptococci groups A and B |
| Viridans streptococci |
| *Clostridium* spp. |
| Diphtheroids |
| Enterococci |
| *Streptococcus bovis* |

## Toxicity

In general, vancomycin is well tolerated. The most common problem associated with its use is phlebitis at the site of the infusion. Frequent intravenous site changes may help to avoid this problem. Fever and maculopapular rash occur in approximately one to three percent of treated patients. More common is the development of urticaria, itching, and at times hypotension immediately following infusion of the drug. This reaction may be confused with anaphylaxis, but it usually does not represent an allergic reaction. The over-rapid infusion of vancomycin leads to release of histamine from mast cells (12). This can be avoided by administering the dose slowly over 30 to 60 minutes.

Ototoxicity appears to be extremely uncommon if serum levels are kept below 80 μg/ml. This is usually quite easy to do, as peak levels should be 25–35 μg/ml and trough levels 10–15 μg/ml. Nephrotoxicity also appears to be uncommon and reversible in subjects receiving vancomycin alone, even when the therapy is continued (4). However, studies done in rats and a retrospective study in humans have both demonstrated that there is a high incidence of nephrotoxicity when vancomycin is used in combination with an aminoglycoside. Over one third of patients treated with the combination developed a significant rise in serum creatinine (4). This suggests that the nephrotoxicity of the two drugs may be additive.

Another often overlooked complication of vancomycin therapy is the development of neutropenia (4). This occurs in 1 to 2 % of patients treated. The

mechanism of this complication is unknown, but most cases appear to be rapidly reversible with cessation of therapy.

### Combination Therapy

Vancomycin is often combined with other antibiotics. There are three major reasons why one or more additional drugs are used in combination with vancomycin. Firstly, the outcome of certain infections appears to be improved, although definitive data are lacking. Secondly, tolerance to vancomycin is fairly common among both staphylococci and streptococci. Thirdly, the poor penetration across the blood brain barrier makes it necessary to use either combination therapy or intrathecal therapy in the presence of central nervous system infection.

There are several important considerations in evaluating the data on combination therapy. In vitro time-kill studies demonstrate that vancomycin and rifampin are antagonistic against *Staphylococcus aureus* (13). However, rifampin is a potent anti-staphylococcal drug, and serum bactericidal activity is often dramatically increased when it is used. In addition, there are anecdotal case reports that demonstrate that certain patients who are unresponsive to vancomycin may respond following the addition of rifampin Therefore, it appears that the clinical outcome may improve with the addition of rifampin despite the in vitro anatagonism. The major role of the vancomycin in this setting is to prevent the development of rifampin resistance, which emerges rapidly when rifampin is used alone. Vancomycin is often combined with an aminoglycoside in the therapy of serious *Staphylococcus aureus* infections. This combination is synergistic in vitro, but clinical data demonstrating any advantage over vancomycin therapy alone are lacking. In addition, this combination is associated with a high incidence of nephrotoxicity. At the present time it seems prudent to treat uncomplicated *Staphylococcus aureus* infections with vancomycin alone, adding rifampin or an aminoglycoside only when there has been a poor response.

The situation is somewhat different with regard to the therapy of *Staphylococcal epidermidis* infections. In vitro studies have demonstrated variable results when the combination of vancomycin and rifampin or vancomycin and an aminoglycoside have been used (14). Although human data are scarce, one retrospective study suggests that vancomycin combined with either rifampin and/or and aminoglycoside may be superior to vancomycin alone in the treatment of prosthetic valve endocarditis. However, the number of cases in this study was small (3). At the present time, a multi-center trial is being conducted to compare the combination of vancomycin and rifampin to vancomycin, rifampin, and two weeks of gentamicin in patients with prosthetic valve endocarditis.

Although data is not available as to the the best therapy for *Staphylococcus epidermidis* catheter-related sepsis, it is my view that most patients do well with a brief course of vancomycin alone.

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